Portland VA Medical Center

Education in the Protection of Human Research Participants

06/14/2002

Overview

- This training module and post-test, supplemented with the successful completion of either the NIH education module or the University of Rochester Medical Center's manual, Protecting Study Volunteers in Research, fulfills the Portland VAMC education requirements in the Protection of Human Research Participants.
- The following topics are covered in this training program
  - Veterans Affairs Research
  - Institution Responsibilities
  - The Assurance and Assurance Process
  - Additional Responsibilities of the Institutional Review Board
  - Conflict of Interest in Research
  - Research involving the use of Human Biological Specimens
  - Emergency use of unapproved Investigational Devices
  - Research involving the use of Medical Records and Pre-Existing Databases
  - Research Related Injury

Education in the Protection of Human Research Participants

- To obtain credit for this education module, please:
  - Review the following pages;
  - Successfully complete the post-test; and
  - Submit the Post-test to the Research Service Office.

Veterans Affairs Research

- Which regulations apply to human research conducted at the VA?
  - All research that is funded, supported by, and/or conducted at a federal institution must adhere to the following regulations:
    - Title 38 - Pensions, Bonuses and Veterans' Relief Chapter 1 - Department of Veterans Affairs Code of Federal Regulations Part 16 - Protection of Human Subjects
    - VA regulations: Manual 3, Part 1, Chapter 9
  - Research that is also funded through the Department of Health & Human Services adheres to:
    - Title 45 - Public Welfare Part 46 - Protection of Human Subjects

Veterans Affairs Research (cont'd)

- Research that also involves investigational drugs or devices adheres to:
  Title 21 - Food & Drug Administration, Department of Health and Human Services
  - Part 50 - Protection of Human Subjects;
  - Part 54 - Financial Disclosure by Clinical Investigators;
  - Part 56 - Institutional Review Board;
  - Part 312 - Investigational New Drug Application; and
  - Part 314 - Applications for FDA approval to market a new drug.

Veterans Affairs Research (cont'd)

Research involving veterans has and needs special precautions to protect our patient population.

- What is unique about our study population?
  - majority are male;
  - majority are 30 years of age and older;
  - some may have health conditions relating to their service in the military, which investigators must keep in mind when recruiting and consenting individuals into studies;
  - some may have problems with substance abuse, which may affect their ability to make an informed decision about participating in research and/or differentiate between standard medical care and research treatments; and
  - some may not have other forms of healthcare coverage so they may feel as though they have to participate in the research to continue receiving healthcare coverage.

PVAMC Institutional Responsibilities

- The PVAMC has the following responsibilities and safeguards, involving the Human Research Program, to protect our human research participants:
  - Establish a Human Research Protection Program (HRPP);
  - Establish and register the Institutional Review Board;
  - Maintain a Research & Development Committee (R&D);
  - Provide adequate administrative staff and space for conducting IRB and research support;
  - Provide Educational Programs; and
  - Provide and Maintain Assurances for Compliance, such as the:
    - Federal Wide Assurance and
    - Investigator Assurances.

Human Research Protection Program

- The Human Research Protection Program (HRPP) defines how human subject research will be conducted at the Portland VA Medical Center and describes the responsibilities of the:
  - Director, the Institutional Official responsible for the HRPP;
  - Associate Chief of Staff, R&D;
  - R&D Committee;
  - Principal Investigators; and
  - Research Service Staff.

- The PVAMC (HRPP) is defined in Medical Center Memorandum MCM 151-01 “Responsible Conduct of Research at the PVAMC.”

Research & Development Committee

- Research & Development Committee (R&D)
- The R&D Committee:
  - is unique to VA institutions;
  - acts as a governing body of the Research Service at a VA institution;
  - is a parent committee to the Institutional Review Board;
  - may not approve any research project that has not been approved by the appropriate subcommittee; and
  - reviews and either approves or disapproves research projects approved by it's subcommittees for the scientific quality of Research and Development projects and for the protection of human research subjects.

Federal Wide Assurance

The Office of Human Research Protections (OHRP) mandates that each institution's Institutional Review Board be registered with the OHRP. Our PVAMC IRB operates under an OHRP approved Federal Wide Assurance (FWA). We, as an institution, must be compliant with the terms set forth in the FWA for protecting human subjects and renew this FWA every three years. The FWA states that our IRB is responsible for abiding by the federal regulations set forth in Title 45 Part 46, regarding the protection of human subjects, and that the Director is the Signatory Official legally authorized to represent the institution.

Investigator Assurances

Each new PVAMC human subjects research project proposal is accompanied by “Investigator Assurances.” They are located on the last page of a research project’s “Initial Review Questionnaire,” and state guidelines set forth by the institution for conducting research projects. This assurance is an agreement that must be signed by the Principal Investigator stating that the PI will abide by the all of the aforementioned guidelines.

Investigator Assurances (cont'd)

Principal Investigators are responsible for ensuring that their research project adheres to all of the assurances. It is vital for an Investigator and their research project to abide by the assurances. When these assurances are not adhered to, they risk research project suspension or termination as set forth by the decisions of the IRB and R&D Committee. These "Investigator Assurances" are detailed in the next slide.

Investigator Assurances (cont'd)

PVAMC Investigator's Assurances:

- I will promptly report proposed changes in the research activity to the IRB and will not initiate these changes until they have been approved by the IRB.
- I will report deaths of VA patients on protocols within **24 hours** to the IRB, and all other serious adverse events (expected or unexpected) or any unanticipated problems involving risk to subjects, to the IRB within **10 days** of occurrence.
- I will forward the original signed consent form to the Research Service office within 72 hours of obtaining the patient's consent. The office staff will take responsibility for assuring that the document is included in the medical record of the subjects. One copy will be maintained in my files and a copy will be given to each subject.

Investigator Assurances (cont'd)

PVAMC Investigator's Assurances (cont'd):

- Since federal regulations require that the study be reviewed periodically, I will take responsibility for maintaining IRB approval, including furnishing the IRB with relevant information when requested.
- I will immediately activate the electronic FLAG for all patients enrolled in this study if the IRB designates this as a project with high or moderate risk.
- I, the undersigned, will be responsible for the ethical conduct of this project and for protecting the rights and welfare of the subjects.

Additional Responsibilities of the IRB

- Among other responsibilities, in addition to reviewing new research projects, the IRB is responsible for:
  - Conducting continuing review of research projects;
  - Reviewing protocol modifications;
  - Addressing and handling violations in protocols and PI non-compliance; and
  - Reviewing and acknowledging research project termination reports.

Continuing Review of Research Projects

- Each research project must be reviewed at least annually by the IRB & R&D Committee. The frequency of review is determined by the IRB and is based on the level of risk that the research project poses to research participants.

- Research projects that are categorized as moderate to high risk may need to be reviewed more often than annually.

Continuing Review of Research Projects (cont'd)

- The IRB evaluates the following criteria at the time of continuing review:
  - research findings to date;
  - changes to the research;
  - adverse event reports;
  - evaluation of risks and benefits to subjects;
  - safety reports, including IND, IDE and MedWatch;
  - protocol violations and/or deviations; and
  - investigator non-compliance, including non-compliance with IRB requirements for frequency of periodic continuing.

Protocol Modifications

- Which changes to a research project need to be reported to the IRB?
  - All changes to a protocol must be reported and approved by the IRB prior to activation.
  - All changes to a consent form must be reported and approved by the IRB prior to use.
  - All changes in research staff must be reported to the IRB.

Protocol Modifications (cont'd)

- What happens if the changes are implemented without IRB approval?
  - If modifications to a protocol or consent form are carried out before the IRB has approved the changes, the IRB has the authority to suspend, suspend with modifications, and/or terminate research projects and/or investigators and staff that are not adhering to the protocol approved by the IRB.
  - If any changes have occurred in your research projects that have not been approved by the IRB, notify the IRB immediately.

PI Non-Compliance

- How is PI Non-Compliance addressed and handled by the IRB and R&D Committee?
  - Violations in research project protocols and PI non-compliance are reviewed by the IRB and R&D Committee.
  - The IRB will investigate the violations and/or allegations of non-compliance, deliberate, and determine what corrective actions need to be implemented.
  - The R&D Committee will approve or disapprove any deliberations made by the IRB.

PI Non-Compliance (cont'd)

- Possible corrective actions regarding protocol violations include research project:
  - Continuation;
  - Continuation with modifications;
  - Suspension; or
  - Termination.

- Possible corrective actions regarding PI non-compliance include:
  - May continue conducting research;
  - May continue conducting research with modifications; or
  - May be suspended from conducting research.

Research Project Termination

- The IRB also reviews and acknowledges research project completion reports.
- Upon completion of research projects, notify the IRB that the research project has been terminated and submit any requested materials for review.
- The IRB is mandated to keep research project files for 3 years from the date of project completion.
- Investigators should maintain research project and patient files for at least 3 years from the date of project completion.
- For all published papers, the primary data published must be stored for at least 5 years.

Conflict of Interest

What is conflict of interest?

- A conflict of interest exists when either a significant financial interest or personal interest could directly and significantly affect the design, conduct, or reporting of a sponsored research project.
- A significant financial interest refers to individuals, their spouses and dependent children having interest in anything of monetary value, including, but not limited to the following:
  - Payment for services: salary and other forms, such as consulting fees or honoraria;
  - Intellectual Property: patents, copyrights, licensing agreements and royalties; and/or
  - Equity: stock ownership, benefits.

Conflict of Interest (cont'd)

Conflicts of interest should be avoided in research projects to maintain the safety of research participants and highest ethical standards of research projects.

The Research & Development Committee will decide if a conflict of interest exists and if it is of a significant financial interest. The institution will work with the investigator to eliminate conflicts of interest or will otherwise implement procedures to manage and minimize any effects and/or monitor research projects with any conflicts of interest.

Conflict of Interest (cont'd)

The PVAMC promotes full disclosure of any conflicts of interest in research projects. This is maintained through the following:

- IRB members are not allowed to be present during the review and vote of research projects in which they have a conflict of interest, except for clarification on questions that may arise during the review process.
- Investigators inform the IRB of conflict of interests they may have with proposed research projects at the time of initial research project review and in the future if conflicts arise during the research project.
- Consent Forms inform potential research participants if an involved investigator has a financial interest in the study.

Human Biological Specimens in Research

Research using human biological specimens is pertinent to the formulation and advancement of new medical treatments and information.

What is a human biological specimen?

Per VHA Directive 2000-043,

A human biological specimen is any material derived from human subjects, such as:

- blood;
- urine;
- tissue organs;
- hair;
- nail clippings; and
- any other cells or liquids,

whether used for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures.

Human Biological Specimens in Research (cont'd)

- Individuals that donate their tissues face a large number of risks as a result of donating their tissues. Therefore, it is essential to protect these research participants that are donating their tissues for the advancement of science and medicine.
- Some of the potential risks of donating tissues for research due to a loss of privacy and confidentiality, resulting from disclosure of a participants personal information, include:
  - Loss of employment;
  - Loss of medical and/or life insurance and/or benefits;
  - Loss of parental rights;
  - Social stigmatization; and/or
  - Emotional hardship when faced with genetic disorders and/or information.

Human Biological Specimens in Research (cont'd)

- How can researchers protect research participants?
  - Inform participants during the informed consent process of all procedures, uses of their tissues, and risks as a result of the research.
  - Handle and store tissues as stated in IRB approved research protocols.
  - Have VA investigators link clinical data to the specimens at the VA, which limits the number of individuals having access to the data and ensures patient confidentiality.
  - Limit the access and amount of clinical information available to non-VA individuals.
  - Delete all unique patient identifiers when specimens leave the VA for analyzing.

Human Biological Specimens in Research (cont'd)

- Research projects that are planning to collect human biological specimens must inform the research participants what will be done with their tissue.
- Inform patients of the following:
  - Who will have access to their tissue;
  - Who will have access to their data;
  - How will their data and tissue be disposed; and
  - What risks do they face when donating their specimens.

The Human Biological Specimens Informed Consent Form Template and checklist may be accessed through the Research Service office.

Human Biological Specimens in Research (cont'd)

- What information must be present in the human biological specimens informed consent form?

Per VHA Directive 2000-043:

- Whether or not the specimen will be used for future research and allow the subject the choice of how the specimen will be used (any research, research by the PI or other researchers, genetic analysis, research related to a specific area, etc.).
- Whether or not the results of future research, involving the use of the specimen, will be conveyed to the subject.
- Whether or not the subject will be re-contacted after the original study is completed.
- If the subject requests, the specimen and all links to the clinical data will be destroyed.

Human Biological Specimens in Research (cont'd)

- What if Principal Investigators would like to collect tissues now for use in future research projects?
  - Tissues collected for future research use are considered "banked" tissues. These tissues must:
    - be stored in a VA sponsored or VA approved tissue bank and
    - be used only for the procedures that the patient agreed to and were outlined in the signed research consent form.

Human Biological Specimens in Research (cont'd)

- What is a VA sponsored tissue bank?

  Per VHA Directive 2000-043:

  – VA sponsored tissue bank is a tissue repository or storage facility at a VA facility or approved off-site location that adheres to VA regulations. It contains human biological specimens collected under VA-approved research protocols that are under both VA ownership and VA control

- What is a VA approved tissue bank?

  Per VHA Directive 2000-043:

  – VA approved tissue bank is an approved tissue bank located at a non-VA facility and has the appropriate approval from the Chief Research & Development Officer. It also meets standards of a VA sponsored tissue bank. Examples of non-VA sites that may **NOT** be appropriate for tissue banking are: non-academic, for-profit institutions.

Human Biological Specimens in Research (cont'd)

- What if the tissues are to be stored, used and/or analyzed at an institution that is not a VA institution?
  - A Memo of Understanding (MOU) must be written between the VA investigator and non-VA institution that states that
    - the non-VA institution will only use the samples as outlined in the protocol;
    - any remaining specimens will be either destroyed or returned to the VA institution;
    - if the specimens are destroyed, the non-VA institution must certify in writing the destruction the samples; and
    - the remaining specimens may not be kept and/or stored by the non-VA institution.
- The investigator must maintain a copy of the original consent under which the samples were collected, a record of the use of specimens, and the protocols under which they were used.

Human Biological Specimens in Research (cont'd)

- How can data from specimens be maintained?
  - Data is considered to be "linked" when there is any patient identifying information attached to the specimen.
  - When linking clinical data to human specimens, the linking should be completed at the VA by the VA investigators, whenever possible.
  - If non-VA investigators will be viewing the data or if the data will be sent off VA site, all identifying links to the data must be destroyed.

Research involving Medical Records and Pre-existing Databases

- Research involving medical records and other pre-existing databases is an important tool for researchers in collecting information for research projects.
- However, there are special precautions that need to be met to protect the privacy and confidentiality of the individuals' whose records are being accessed and viewed.
- These precautions include:
  - IRB review and
  - Provisions for protecting individuals' information.

Research involving Medical Records and Pre-existing Databases (cont'd)

- Research projects involving the use of medical records and pre-existing databases must be reviewed and approved by both the IRB and R&D Committee.
- The IRB will decide if adequate provisions have been implemented in the research project to protect individuals' personal information.
- Without adequate provisions to protect these individuals, they may be at risk due to a loss of privacy and confidentiality, resulting from disclosure of the participants personal information. The potential risks include:
  - Loss of employment;
  - Loss of insurance and/or benefits; and/or
  - Social stigmatization.

Research involving Medical Records and Pre-existing Databases (cont'd)

- What should investigators consider when making adequate provisions to protect individuals?
  - Limit the amount of identifying information collected from records and databases;
  - Limit the individuals who will be accessing and analyzing the data;
  - Use encryption and other codes to link the research data to the subject identifiers;
  - Include adequate procedures for destroying the documents and data; and
  - Train research staff that will be working with the data about the importance of maintaining the individuals' confidentiality.

Research involving Medical Records and Pre-existing Databases (cont'd)

Which research projects involving records based research do not need an informed consent form?

- A waiver from the informed consent requirement or an alteration of an element from the informed consent requirement may apply to research projects only if all of the following are met:

  Per 38CFR16

  - The research involves no more than minimal risk to the subjects, and
  - The waiver or alteration will not adversely affect the rights and welfare of the subjects, and
  - The research could not practicably be carried out without the waiver or alteration, and
  - The subjects will be provided with additional pertinent information after participation.

  Note: the IRB will make the final decision as to whether or not the informed consent requirement may be waived from a research project.

Research Related Injury

- Definition - an injury to a research participant that is a direct result of the research.
- All research projects that are categorized as more than minimal risk must offer an explanation to research participants in the consent form, explaining that if they are injured as a cause of the research whether or not:
  - compensation will be available if injury occurs AND
  - medical treatment will be available, and if so, then
    - how medical treatment will be available and
    - the extent of medical treatment.
- If a research participant is injured as a direct result of the research, report the incident immediately to the IRB.

Summary

- This education module has covered the following topics specific to Research involving human research participants at the PVAMC:
  - Veterans Affairs Research: Applicable federal regulations and characteristics of our unique patient population.
  - Institution Responsibilities: Human Research Protection Program; R&D Committee; IRB and education programs.
  - The Assurance and Assurance Process: OHRP mandated Federal Wide Assurance and Investigator Assurances.
  - Additional Responsibilities of the Institutional Review Board: conducting continuing review and reviewing and deliberation of protocol modifications, PI non-compliance, and research termination reports.

Summary (cont'd)

- Conflict of Interest in Research: full disclosure of personal and significant financial interests.
- Research involving the use of Human Biological Specimens: Types of human biological specimens; banked specimens are to be kept at VA approved or sponsored facilities; informed consent form requirements; and risks of the loss of privacy and confidentiality of patient information.
- Research involving the use of Medical Records and Pre-Existing Databases: risks of loss of privacy and confidentiality of patient information and requirements from the waiver of informed consent.
- Research Related Injury: Informed consent requirement for studies with more than minimal risk to the participant.

Summary (cont'd)

Congratulations!

- You have now completed the PVAMC Education in the Protection of Human Research Participants Training Module. Please print and complete the following post-test. Then submit your test to the Research Service office. We will notify you with your results.
- If you have any questions regarding the material in this training module, please do not hesitate to contact:

Angie Lacey
Research Assurance & Compliance Coordinator
angela.lacey@med.va.gov
laceya@ohsu.edu
503.220.8262 ext. 51165

Education in the Protection of Human Research Participants
PVAMC Module Post-test

1. The PVAMC Institutional Review Board operates under an approved Federal Wide Assurance.
   - ☐ True
   - ☐ False

2. Which government agency mandates this FWA? Please check the correct one below.
   - ☐ Department of Veterans Affairs
   - ☐ Office of Human Research Protections
   - ☐ Food & Drug Administration

3. Investigators agree to which of the following procedures when they sign the "Investigator Assurances," the last page of the Initial Review Questionnaire, submitted with all new research project proposals? Please check all that apply.
   a. ☐ I will forward the original signed consent form to the Research Service office, within 72 hours of obtaining the patient's consent. One copy will be maintained in my files and a copy will be given to each subject.
   b. ☐ I will be responsible for the ethical conduct of this project and for protecting the rights and welfare of the subjects.
   c. ☐ I will promptly report proposed changes in the protocol activity to the IRB and will not initiate these changes until they have been approved by the IRB.
   d. ☐ I will immediately activate the electronic research FLAG for all patients enrolled in this study if the IRB designates this as a project with high or moderate risk.

4. Which of the following, a or b below, is true regarding the type of protocol modifications that need to be reported and approved by the IRB prior to activation?
   a. ☐ Only major protocol modifications
   b. ☐ All protocol modifications

5. According to federal regulations, a conflict of interest exists in a research project sponsored by a pharmaceutical company when the Clinical Investigator owns a significant amount of stock in the pharmaceutical company that is sponsoring the study.
   - ☐ True
   - ☐ False

6. According to the Veterans Health Administration, which of the following are considered human biological specimens? Please check all that apply.
   a. ☐ skin biopsy
   b. ☐ blood
   c. ☐ finger nail clippings
   d. ☐ urine

7. Human biological specimens are considered "banked" if they are being stored for future research purposes.
   - ☐ True
   - ☐ False

8. According to VHA regulations, which of the following is **not** an appropriate facility to store PVAMC research patients' human biological specimens?
   a. ☐ Portland VA Medical Center
   b. ☐ pharmaceutical company
   c. ☐ a non-VA facility that has been approved by the Chief Research & Development Officer
   d. ☐ a VA sponsored medical center

9. Research projects that will be collecting human biological specimens must comment on which of the following in the informed consent form? Please check all that apply.
   a. ☐ Release of research results to the subject, following the reuse of the specimen.
   b. ☐ Whether or not the subject will be re-contacted after the original study is completed.
   c. ☐ A statement that the specimen and all links to the clinical data will be destroyed if the participant would like.
   d. ☐ A statement that the investigator may reuse the specimens for **ANY** unspecified future research.

10. Investigators that would like to perform a review of PVAMC hospital paper records do **not** need IRB and R&D Committee approval.
    ☐ True
    ☐ False

11. Investigators that would like to perform a review of the PVAMC electronic medical records or electronic databases do **not** need IRB and R&D Committee approval.
    ☐ True
    ☐ False

12. According to the Federal Code of Regulations, 38CFR16.116, which records-based research project may qualify for a waiver of the informed consent requirement? Please check all that apply.
    a. ☐ Research that involves a significant risk to individuals.
    b. ☐ Research that could not be carried out without the waiver of informed consent.
    c. ☐ Research that is of only minimal risk to the individual.
    d. ☐ Research that will not negatively affect the welfare of the individual.

_____ _____
Name Research Related Position Title

_____ _____
Signature Date

_____ _____
E-mail Name of PI

Please complete and submit this post-test to the Research Assurance & Compliance Coordinator, Angie Lacey, in the Research Service Office. The Research Service will notify you of your certification.

Mail stop: R&D

Office Use Only: Score:_____ Pass: ☐ Yes ☐ No